DETAILED ACTION

Claims 5, 7-9, 26, 29, 31, 37, 48-51, 56, 58, 70, 72, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150 and 156, 158-159, 161-169 are pending. Claims 147, 150, 162-163 remain withdrawn.

Applicants' arguments filed on 06/27/2011 have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejection- 35 U.S.C 112 Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 5,7-9, 26 ,29,31,37,48-51,56, 58,70,72,76,78,108, 110117,127-129,131-134,156,158,159 and 161, 164-167 (depend on claim 1) , 168 and 169 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claim 1 and 168-169 introduce new matter in reciting "the polypeptide is not fibrin" and "with the proviso that the protease domain is not urokinase plasminogen activator". Introduction of "the polypeptide is not fibrin" and "with the proviso that the

protease domain is not urokinase plasminogen activator" in the claims is a new matter because neither the specification nor the claims as originally filed disclose these exclusions as preferred embodiments of the claimed invention. The Examiner has not been able to find support in the specification for the recited exclusions, i.e., " the polypeptide is not fibrin" and "with the proviso that the protease domain is not urokinase plasminogen activator. Thus, there is no indication that the current claims were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

Argument

Applicants' argument is considered but found unpersuassive because the specification doest not have support for the recited exclusions.

Moreover applicants argument that they can freely choose any embodiment from the specification to be entered in the claim, especially to avoid the prior art rejection, in any time in the prosecution is found unpersuasive. Species selection has to be made initially at the beginning of the prosecution of the case during election/restriction. Furthermore for species selection all the species should be in the claim in 1st place and applicant should elect a species for examination

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a)A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 remain rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, matrix metalloprotease, etc) which catalyze degradation of a specific target are conjugated to binding partner such as, protein or peptide or an antibody (immunoglobulin, Fab, $F(ab)_2$ claim 27), wherein said fusion protein has greater (catalytic or more than one,) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target polypeptide and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. Davis et al. chimeric protein is chemically cross-linked fusion protein not a cotranslation fusion protein encoded by a recombinant nucleic acid made by of respective genes. Protein conjugates can be made either by chemical conjugation or by gene fusion methods (applicants specification page 2 lines 26-30), but gene fusion methods have some particular advantages (see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577). It is well known in the prior art how to make fusion proteins by translation of a chimeric gene fusion (such as references supplied in the amendment of 5/7/08 by the applicants and also Bhatia et al Intl. J. Cancer 2000, 85,

571-577). Bhatia et al teach antibody-targeted enzymes made by the gene fusion method. Therefore, one knowledgeable in prior art is **motivated** to make the protein conjugate of Davis et al by gene fusion methodology as taught by Bhatia et al.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein of Davis et al. by the method Bhatia et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide. Claims 70, 72, 76, 78, 165 is included in rejection because of the reasons explained below: Claim 165 requires the substrate polypeptide from specific target such as, protein aggregate cleaved by a protease or a specific protease such as a metalloprotease, which is taught by Davis et al. The fusion protein of Davis et al cleave peptide bonds of any substrate polypeptide in a blood stain or milk stain (paragraph 0067) which can be regarded as protein aggregate. With regard to claims, 70, 72, 76, 78, Davis et al teach that the substrate can be receptors, signaling molecules like cytokines, EGF-like factors, etc., which are compounds found in a biological fluid of an animal, including blood.

Argument

Applicants' argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach the advantage of chemical cross-linking and therefore one will not motivate to use a cotranslation gene fusion technique. Applicants' arguments have been fully considered, but they are found unpersuasive. It is well known in the art that protein conjugates can be made either by chemical conjugation or by gene fusion methods (applicants specification page 2 lines 26-30), but

gene fusion methods have some particular advantages (see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577). Bhatia et al (Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) provide motivation to make a fusion protein by gene fusion method as they teach the advantages of the recombinant fusion protein such as easier to make, a well-defined product obtained, and a higher purity product compare to chemical conjugation. Thus one of ordinary skill in the art would have been **motivated** at the time of invention to make a protein conjugate comprising the protein partners of Davis et al by gene fusion methodology (as taught by Bhatia et al.)

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) as described above, and further in view of Tamburini et al (US PAT 5,981,208)).

Davis et al. and Bhatia et al are described above. However neither Davis et al., nor Bhatia et al et al. teach the said substrate is from amyloid deposit.

Tamburini et al teach the use of secretase (a metalloprotease, column 2) which catalyse the proteolytic cleavage of amyloid protein precursor in amyloid deposit (column 2) for the detection of Alzheimer's diseases. Detection of Amyloid deposit or amyloid protein precursor is important to diagnose Alzheimer's disease (Tamburini et al column 1)

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein comprising secretase conjugated to an antibody molecule that binds to the amyloid protein precursor in an amyloid deposit by the method as taught by Davis et al., and Bhatia et al and use the resulting adzyme to detect likelihood of Alzheimer's diseases by cleaving amyloid protein.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of, Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) as described above, and further in view of Dolinar et al. (*Food tecnol and biotech.* 2000, 38, 5-9)..

Davis et al. and Bhatia et al are described above. However neither Davis et al., nor Bhatia et al et al. teach purification of a fusion protein comprising a protease domain using a reversible protease inhibitor.

Use of protease inhibitor in protein purification is well known in prior art. Dolinar et al. teach MMTS (methyl methane-thiosulfonate), a reversible protease inhibitor in the purification and refolding of a cysteine proteinase type protein (page 6, column 2 last parg.). Therefore, one of skill in the art would have been **motivated to** purify **a** fusion

protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease.

As such it would have been obvious to one of ordinary skill in the art to use a protease inhibitor to purify the protease-containing fusion protein complex of Davis et al described above. One of ordinary skill in the art has a reasonable expectation of success at obtaining an adzyme which is resistant to autocatalytic proteolysis in view of the teachings of Dolinar et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above but not found to be persuasive.

Claims 49-50, 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Bhatia et al and further in view Steinhauer et al (Virology 1999, 258, pp 1-20).

Davis et al. and Bhatia et al. are described above

Steinhauer et al teach that activated hemagglutinin is essential for infectivity because it allows virus particles to attach to cell receptors and it also mediates fusion of the viral and cellular membranes (page 2, right column, first full paragraph) Inactivation

of virus such as the influenza virus is of major medicinal importance (see Steinhauer et al.; introduction). One of skill in the art would clearly understand that proteolytic degradation of the **activated** hemagglutinin so that it no longer can be used to attach viral particles to cell receptors or mediate fusion of viral and cellular membranes would reduce infection because of the role of the activated protein in viral infectivity.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein comprising protease conjugated to influenza virus specific antibody molecule by the method as taught by Davis et al., and Bhatia et al and use the resulting adzyme to inactivate influenza virus type substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptides.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above.

Claims 56, 110, and 167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Bhatia et al and further in view Schooltink et al (J. Interferon and Cytokine Res 2002, 5, 505-516).

Davis et al. and Bhatia et al. are described above

However, neither Davis et al., nor Bhatia et al. teach a fusion protein that inhibit binding of TNF-alpha to TNF-alpha receptor.

Schooltink et al (J. Interferon and Cytokine Res 2002, 5, 505-516) teach TNFR (page 508) and also teach the importance of TNF-alpha receptors in inflammatory diseases. and drug development. One of skill in the art know that pro-inflammatory molecule TNF-alpha play a key role in inflammatory diseases (Page 508, Schooltink et al). Degrading TNF-alpha by protease will decrease inflammatory response. It is well known in the art that TNF-alpha bind to cell surface receptors such as p55 (Schooltink et al page 508). Therefore one of skilled in art is motivated to use a fusion protein which comprise a protease domain and a targeting domain that bind on p55 TNF alpha receptor so that protease domain could cleave the TNF-alpha molecule in order to treat inflammatory diseases.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein of Davis et al. by the method Bhatia et al. and use the resulting adzyme to inactivate substrate polypeptides in TNF-alpha by catalyzing the proteolytic cleavage of the said substrate polypeptide to decrease inflammation.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above.

Claims 26, 29, 31, 159, 161 and 165-166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) further in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463).

The teachings of Davis et al., and Bhatia et al described above. However Davis et al. nor Bhatia et al teach the use of a linker in between the catalytic domain and the binding domain.

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment thereof or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$. Guo et al also teach the advantage of $(Gly_4Ser)_3$ as a linker, such as enhanced hydrophilicity and conformational flexibility (page 457, column 1 2nd paragraph). Therefore, one of ordinary skill in the art is motivated to make a fusion protein (as taught by Davis et al.) wherein an enzyme (serine protease which catalyze the degradation of a specific target) is conjugated to an antibody (immunoglobulin which binds to the target) by $(Gly_4Ser)_3$ type linker.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein as taught by Davis et al by fusing serine protease which catalyze the degradation of a specific target to an antibody *via* a linker as taught by Guo *et al.* and use the resulting fusion protein to inactivate polypeptide substrates by catalyzing the proteolytic cleavage of the said polypeptide substrates.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above.

Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., and Bhatia et al in view of Debburman *et al.* (PNAS 1997 94, 13938-13943). This rejection is maintained as discussed at length in the previous office action and discussed it again.

The teachings of Davis et al., and Bhatia et al are described above. Davis et al., and Bhatia et al do not teach use of their fusion protein to degrade target comprising prion protein molecule.

Debburman et al. teach prion proteins comprise protease labile PrPc and protease resistant, PrPSc. Debburman et al. also teach that a protease labile prion protein converts to protease resistant, PrPSc. Protease resistant form of prion (PrPSc , page 13938 column 1, 2nd paragraph) is involved in diseases. Therefore, one of ordinary skill in the art is motivated to make fusion proteins as taught by Davis et al., and Bhatia et al. comprising enzymes (protease) conjugated to binding partners wherein the binding partner is an antibody specific to a prion molecule and use it to catalyze the degradation of the prion molecule before it turn into the resistant form.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein comprising protease conjugated to prion specific antibody molecule by the method as taught by Davis et al., and Bhatia et al and use the resulting adzyme to

inactivate prion type substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate prion polypeptides.

Argument

Applicants argument is considered as explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above.

Claims 131-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., and Bhatia et al in view of Sanderson et al. (Medic. Res Rev 1999)..

The teachings of Davis et al., and Bhatia et al are described above.

However, Davis et al., and Bhatia et al do not teach said a pharmaceutical preparation comprising a reversible inhibitor safe to humans.

Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197) teach a small molecule non-covalent binding protease inhibitor that used with a pharmaceutical composition which is reversible and safe in humans (abstract).

Use of protease inhibitors in a protein sample is well known in the prior art because proteases auto catalyze their own degradation (Sanderson et al). In order to extend the life of pharmaceutical preparation comprising the fusion protein and to preserve its effectiveness in humans, one of ordinary skill in the art is motivated to add a reversible protease inhibitor which is safe to humans (as taught by Sanderson et al). As such it would have been obvious to one of ordinary skill in the art to make

pharmaceutical preparation comprising a fusion protein as taught by Davis et al., and Bhatia et al and combine it with a reversible protease inhibitor as taught by Sanderson et al. so that said inhibitor is safe for humans and the pharmaceutical preparation is effective.

Argument

Applicants argue that one of ordinary skill in the art would not combine Davis et al., Bhatia et al and Sanderson et al. (Medic. Res Rev 1999). to reject applicants claims 131-134. Applicants argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach the advantage of chemical cross-linking and therefore one will not motivate to use a cotranslation gene fusion technique that applicant use in their invention. Applicants argument against the use of Davis et al and Bhatia et al is considered and elaborately explained against argument for the rejection of the Claims 5, 7-9, 37, 70, 72,76, 78, 108, 117, 127-129, 156, , 164-165 rejection under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57, IDS) above. Therefore as independent claim 5 is obvious under 35 USC 103, dependent claims 131-134 are also obvious under 35 USC 103.

Double Patenting Rejection

The provisional rejection of claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119 and 127-29, 131-134 under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 1, 4-5, 19-27, 30-34, 37-41 of copending Application No.10/792498 and 10/650,591 is maintained.

Examiner agrees with applicant that the provisional double patenting rejections may be withdrawn when all claims are otherwise and the "provisional" **double patenting rejection in the instant application is the only rejection** remaining, the examiner will withdraw this rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the application issues as a patent. All the examined claims of the instant application have been rejected on other grounds. Since applicant did not submit terminal disclaimer, the rejections are maintained.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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8/26/11